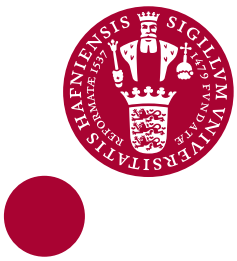

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Published in:
Acta Paediatrica

DOI:
10.1111/apa.14480

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

Low-saturated-fat and low-cholesterol diet does not alter pubertal development and hormonal status in adolescents

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Keywords
Dietary counselling, Low-cholesterol diet, Low-saturated-fat diet, Puberty, Sex hormones

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Received
1 February 2018; revised 19 April 2018; accepted 26 June 2018.

DOI:10.1111/apa.14480

ABSTRACT

Aim: The aim was to assess the influence of dietary counselling on the pubertal development and hormonal status in healthy adolescents.

Methods: We used a subcohort of 193 healthy boys (52%) and girls (48%) from the Special Turku Coronary Risk Factor Intervention Project. Participants were recruited by nurses at the well-baby clinics in Turku Finland in 1990–1992 and randomised into intervention and control groups. Intervention children received low-saturated fat and low-cholesterol dietary counselling initiated at seven months of age. Participants were examined once a year with Tanner staging, anthropometric measurements and serial reproductive hormones from 10 to 19 years of age. In girls, postmenarcheal hormones were not analysed.

Results: Pubertal hormones in boys or girls did not differ between the intervention and control groups. However, we observed slight differences in pubertal progression by Tanner staging and in anthropometric parameters. The intervention boys progressed faster to G4 ($p = 0.008$), G5 ($p = 0.008$) and P5 ($p = 0.03$). The intervention boys were taller than control boys ($p = 0.04$), while weight and body mass index did not differ.

Conclusion: Dietary intervention did not affect pubertal hormonal status. This finding supports the safety of implemented counselling in respect to puberty.

INTRODUCTION

The Special Turku Coronary Risk Factor Intervention Project (STRIP) was launched in 1989 as a prospective, randomised, case–control study aiming to assess the impact of early-onset dietary and lifestyle intervention on the development of atherosclerosis in early adulthood (1,2). Interventional counselling emphasised low-saturated-fat and low-cholesterol diet, which was initiated among the intervention group infants at the age of seven months and maintained through childhood and adolescence (3).

Until now, the STRIP study has produced strong evidence that low-saturated-fat and low-cholesterol diet during childhood and adolescence has no negative effects on growth and development of intervention children (3). Simultaneously, the follow-up of the intervention group has revealed a reduction in cardiometabolic risk factors with clear beneficial effects on serum cholesterol values especially in boys and a protective antiatherosclerotic effects during young adulthood (1–7). The STRIP study has shown that the repeated dietary counselling is effective in decreasing saturated fat intake and leads to lower serum low-density lipoprotein cholesterol concentration from infancy until 19 years of age (6). Additionally, the

Abbreviations
DISC HAS, The Dietary Intervention Study in Children and The Hormone Ancillary Study; STRIP, The Special Turku Coronary Risk Factor Intervention Project.

Key notes

- Little is known about the impact of low-saturated-fat and low-cholesterol dietary counselling during childhood on pubertal development and sex hormones.
- This study showed that low-saturated-fat and low-cholesterol dietary intervention did not alter pubertal development or reproductive hormones in healthy boys and girls.
- Thus, such intervention seems to be safe and our results should encourage for the implementation of this dietary counselling in general practice.

intervention has been associated with improved insulin sensitivity, lower blood pressure, enhanced brachial artery endothelial function, increased ideal cardiovascular health score and a reduced risk for the metabolic syndrome (8–12).

The influence of environmental and dietary factors on pubertal development and timing of puberty is one of the topics of current interest in this field of paediatric research (13–15). Previous STRIP research has found no difference in pubertal timing between the intervention and control groups (3). However, dietary fat intake may influence sex hormone concentrations in adults (16,17).

There is very limited information about the effects of low-saturated-fat and low-cholesterol diet on pubertal development. We hypothesised that this diet is safe in respect to puberty and decided to perform the ancillary analysis of pubertal hormones in a subcohort of STRIP to prove this.

SUBJECTS AND METHODS

The original prospective randomised STRIP cohort was recruited by nurses at the well-baby clinics in the city of Turku Finland between 1990 and 1992. The initial cohort of 1062 healthy children was allocated to intervention (n = 540) and control (n = 522) groups by random numbers at seven months of age. Randomisation was carried out blindly by an independent person. The required sample size for the trial was predicted to achieve, at a 1% significance with 80% power, a 0.2 mmol/L true difference in the change of serum cholesterol concentration between the study groups, assuming that the SD of serum cholesterol concentrations is 0.9 mmol/L. The main aim of the dietary counselling in the intervention group was to achieve a fat intake of 30–35% of daily energy, cholesterol intake <200 mg/day and an intake ratio of saturated/unsaturated fatty acid of 1:2. The intervention started at the age of seven months and continued through childhood and adolescence at the Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku. Anthropometric variables (height, weight, body mass index) were assessed annually at every research visit and pubertal status (Tanner staging) from age nine years onwards. Tanner staging included an assessment of breast development in girls by palpation and measurement of breast tissue with a ruler (B), assessment of external genitalia in boys by measuring the length of the testes with a ruler (G) and assessment of pubic hair (P). The onset of puberty (G2 in boys) was considered to occur when testicular length was more than 2 cm. The physical examination of participants was performed by less than five trained study nurses who were trained by an experienced paediatric endocrinologist. Food consumption was recorded using a four-day food record. A nutritionist checked the food records for accuracy, and the nutrient intakes were analysed with the Micro Nutrica software (The Social Insurance Institution, Turku, Finland). The program calculates 66 nutrients in commonly used foods and dishes in Finland. For more detailed description of the original cohort, we are referring to previous STRIP publications (1–3).

The aim of this study was to analyse pubertal hormones in STRIP participants. The subgroup consisted of a randomly selected subcohort of 200 STRIP children, in whom continuous anthropometric data through childhood as well as blood samples for hormonal analyses were available. A fasting venous blood sample was collected for hormonal measurements once a year from 10 to 19 years of age. Serum levels of oestradiol, follicle-stimulating hormone, luteinising hormone and sex hormone-binding globulin were determined in girls. Pubertal hormonal follow-up in girls was continued only until menarche, because blood samples were not standardised by menstrual cycle. In boys, serum levels of testosterone, follicle-stimulating hormone, luteinising hormone, sex hormone-binding globulin, anti-Müllerian hormone and inhibin B were measured. Anthropometric variables and Tanner staging were also assessed once a year starting at nine years of age according to the general STRIP protocol (2).

All blood samples were fasting and they were obtained at standardised morning time. After clotting and centrifugation, serum was stored at −75°C until hormone analyses were performed. All serum samples were analysed blinded at the Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark. The concentration of oestradiol was measured using radioimmunoassay (Pantex, Santa Monica, CA, USA) with a detection limit of 18 pmol/L and an interassay coefficient of variation below 15% in the low range. Follicle-stimulating hormone and luteinising hormone were determined by two-sided fluoroimmunometric analysis the AutoDELFIA (Wallac Oy, Turku, Finland) with detection limits of, respectively, 0.06 and 0.05 IU/L and interassay coefficients of variation below 5%. Sex hormone-binding globulin, testosterone and anti-Müllerian hormone concentrations were measured by chemiluminescent enzyme immunoassays the Access 2 (Beckman Coulter, Brea, CA, USA) with detection limits of 0.33, 0.35 and 0.14 pmol/L, respectively, and interassay coefficients of variation below 6%. Inhibin B was determined by a specific two-sided enzyme-linked immunoassay the Inhibin B gen II (Beckman Coulter) with a detection limit of 3 pg/mL and an interassay coefficient of variation below 11%. Free testosterone was calculated using total testosterone and sex hormone-binding globulin values with a fixed albumin value by the method described by Vermeulen et al. (18).

Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and R statistical package, version 3.2.3 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). In the analysis of hormonal, anthropometric, cholesterol and dietary variables, mixed models for repeated measures was used to account for missing values. The interaction between age and treatment was analysed with all the response variables. After checking of the normality of the distributions among the response variables, only follicle-stimulating hormone in the boy cohort needed log transformation. Fisher's exact test was applied to compare the difference in percentages of the control and intervention children who entered puberty at a certain age. In the comparison of two

independent groups, Student's *t*-test was used. A two-tailed $p < 0.05$ was considered statistically significant.

The study was approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital. The study was performed according to the Helsinki II declaration. Informed consent was obtained from all participating families in the beginning of the study and again from the participants at 15 years of age. This trial was registered on www.clinicaltrials.gov. The unique identifier is NCT00223600.

RESULTS

Altogether 193 participants were included in the final analyses. Of these 104 (50% boys) were from the control group and 89 (54% boys) from the intervention group. We did not find any statistically significant differences in the levels of pubertal hormones between the intervention and control participants in either sex (Figs 1 and 2, Tables S1 and S2). Intervention boys were taller ($p = 0.04$) than control boys with no difference in weight and body mass index (Fig. S1, Table S1). The percentages of the children who entered puberty by a certain age are shown in Table 1. The dynamics of pubertal maturation (age at attainment of a certain Tanner stage) in both study groups and genders are shown in Tables S3–S6. The intervention boys showed a tendency to reach Tanner stages 4 and 5 earlier than control boys. The mean age at Tanner G4 in intervention and control groups was 14.0 and 14.7 years, respectively ($p = 0.008$). The mean age at Tanner G5 was 15.8 and 16.4 years, in intervention and control groups, respectively ($p = 0.008$). Moreover, the intervention boys reached Tanner P5 earlier than controls, at 15.2 and 15.8 years, respectively ($p = 0.03$). However, further hormonal analysis aiming to find an interaction with Tanner stages (G) did not reveal any differences between the study groups of boys. The age at menarche did not differ between the intervention and control girls (12.9 years in both groups, $p = 0.95$). Tanner stage G2 in boys and B2 in girls was the first sign of puberty in most participants, and there was no difference between the intervention and control groups in the proportion of participants who progressed to P2 before G2/B2 ($p = 0.23$ and $p = 1.0$ for boys and girls, respectively).

In these boy and girl subcohorts, both serum cholesterol concentrations ($p = 0.005$ and $p = 0.03$, respectively) and saturated fat intakes ($p < 0.001$ and $p = 0.002$, respectively) were lower in the intervention group than in controls (Figs S1 and S2).

DISCUSSION

To our knowledge, our project was the second attempt to assess pubertal hormones in a group of children receiving a low-saturated-fat and low-cholesterol dietary intervention. However, our project was the first such analysis performed on children representing general unselected population.

The conversion of androgens into oestrogens by fat tissue may theoretically influence pubertal timing and development. Wang et al. (19) showed a positive association between obesity and sexual maturation in girls. Simultaneously, in boys, the association was inverse. Other fat-derived signals (leptin) and body size-linked signals (insulin-like growth factor 1) play an essential role for timing and progression of puberty as well. However, the precise role of these hormonal factors is not known (13). Dietary restrictions during childhood and adolescence may potentially disturb all signals mentioned above.

Changes in pubertal timing and altered hormonal status during puberty may have long-term consequences, for example the increased risk of cancer later in life. Breast cancer risk is inversely associated with the age of menarche and testicular cancer risk is inversely related to the age at male puberty. A higher risk of metabolic syndrome, obesity, type 2 diabetes and cardiovascular disease in adulthood is associated with premature adrenarche. Altered timing of puberty is linked with many other undesirable conditions and diseases during childhood and in adult life (behavioural disorders) (20).

We mentioned previously that STRIP was the second study evaluating pubertal sex hormone levels in a group of children receiving a low-saturated-fat and low-cholesterol dietary intervention. In contrast to the first study investigating the same aspect (The Dietary Intervention Study in Children and The Hormone Ancillary Study or the DISC HAS), we did not find differences between the intervention and control children in physical pubertal development or in pubertal hormonal status. However, in STRIP, we only analysed hormones in girls until menarche, whereas in the DISC HAS project, the hormonal analyses revealed differences in postmenarcheal participants. Postmenarcheal DISC HAS girls in the intervention group had circa 20–30% lower oestradiol, non-sex-hormone-binding globulin-bound oestradiol, estrone and estrone sulphate levels during the follicular phase of the menstrual cycle and 27.2% higher testosterone levels during the luteal phase of the menstrual cycle, than did girls in the usual care group. The luteal phase progesterone level was 52.9% lower for postmenarcheal DISC HAS girls in the intervention group than for girls in the usual care group (21). In boys, neither our study nor DISC HAS found any hormonal differences during pubertal development (22). As we did not have information on the phase of menstrual cycle in postmenarcheal girls, we could not analyse properly the hormone values from this period.

Our data suggested some subtle, statistically nonsignificant differences between the intervention and control groups more pronounced in boys than in girls. In the male intervention cohort, the height, growth and pubertal hormonal activation started slightly earlier than in control (Figs 1 and S1 and Table S1). In contrast, in the girl cohort, pubertal hormonal activation began slightly earlier in the control group than in the intervention group (Figs 2 and S2 and Table S2). These observations need further corroboration. However, they are interesting from a public health perspective, as we still do not know the cause for the currently observed earlier onset of puberty in many

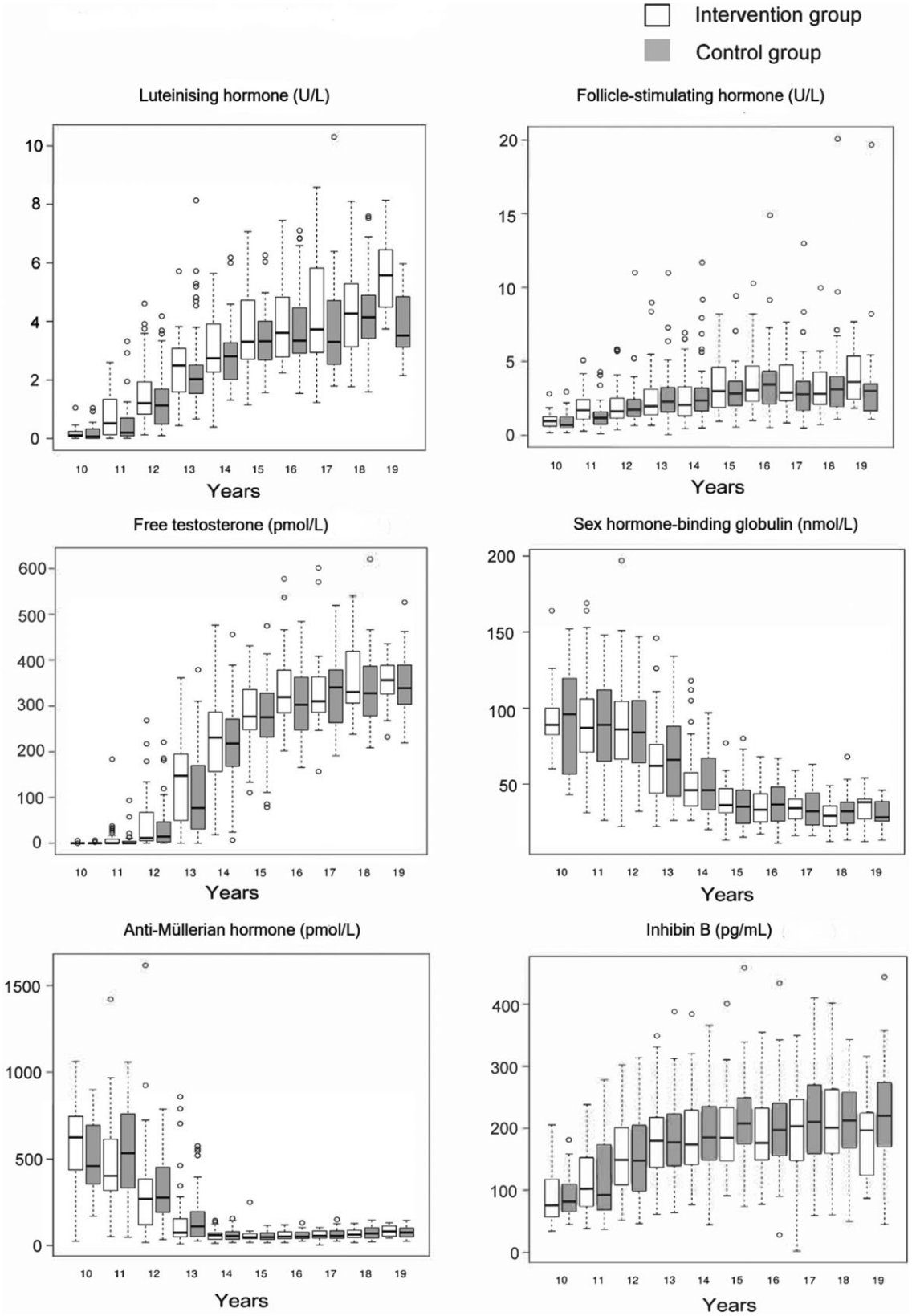

Figure 1 Hormone levels in the boy cohort.

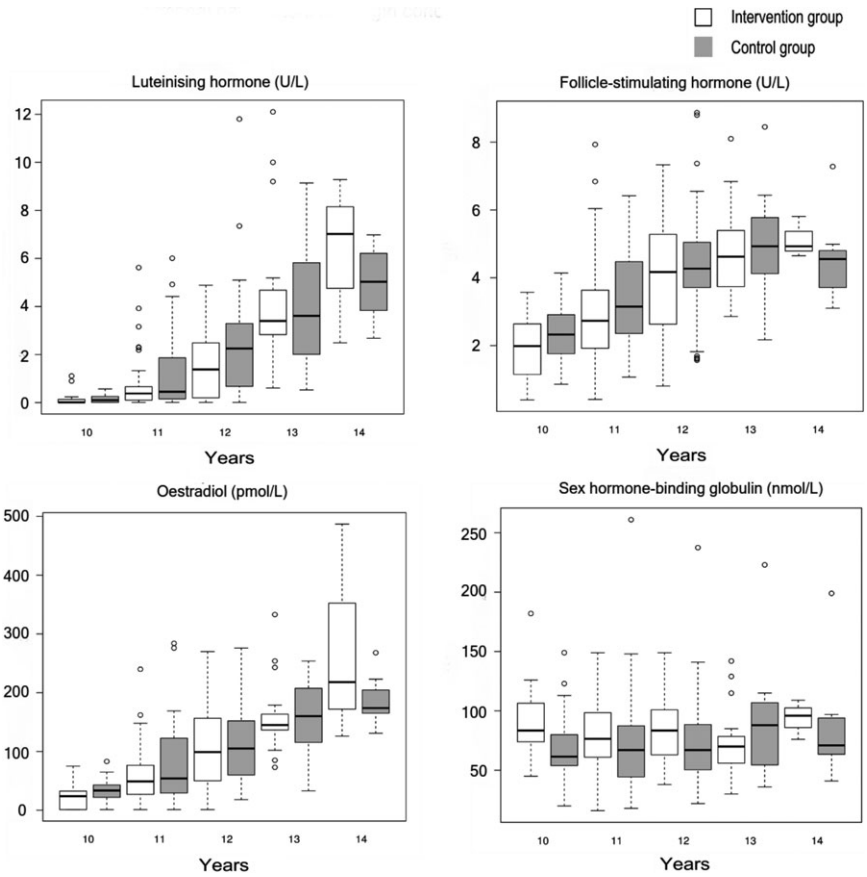

Figure 2 Hormone levels in the girl cohort.

Table 1 Proportion of children who have entered puberty

	By 10 years,%	By 11 years,%	By 12 years,%	By 13 years,%	By 14 years,%
Boys (p = 0.07)					
Intervention	7	66	88	98	100
Control	11	42	82	100	100
Girls (p = 0.24)					
Intervention	18	42	85	100	
Control	15	60	88	100	

Boys: Tanner > G1P1; Girls: Tanner > B1P1.

countries. In our opinion, the most reasonable explanation of this finding could be different body composition in intervention and control children, that may influence their hormonal status.

The lack of postmenarcheal hormonal data and smaller number of participant are the main disadvantages of our study compared to DISC HAS. At the same time, the STRIP cohort has several advantages compared to the previous study. In our opinion, our results are more generalisable than those of DISC HAS. During the STRIP recruitment, the baseline cholesterol level was not a criterion for inclusion in the project. Thus, STRIP participants represent the general population. Furthermore, the STRIP intervention started at seven months of age resulting in longer intervention period. The regular annual assessment was performed throughout the intervention period. In the DISC HAS project, only children with elevated levels of low-density lipoprotein cholesterol were recruited in prepuberty (23). Eligible girls were 7.8–10.1 years old and boys 8.6–10.8 years old. During follow-up, hormonal and anthropometric parameters were assessed only 5 times: at baseline, after one, three and five years and at the last visit (23). In addition, dietary aims in DISC HAS were stricter than in STRIP. Dietary interventional goals in the DISC HAS

project were to promote adherence to a diet providing 28% of energy from total fat, less than 8% from saturated fat, up to 9% from polyunsaturated fat and less than 75 mg/4200 kJ (1000 kcal) per day of cholesterol (not to exceed 150 mg/day) (23). In STRIP, the aim was to provide 30–35% of daily energy from fat and less than 10% of daily energy from saturated fat (1).

We also have to acknowledge the general limitations of our study. Firstly, the study results could be potentially affected by the incomplete hormonal data, as the analysis of sex hormones was performed only in subcohort of 200 STRIP participants. However, in the present study, the anthropometric outcomes, timing of attainment of Tanner stages and menarcheal age were close to those in the total STRIP cohort. Lower total cholesterol and saturated fat intake values in the intervention boys and girls compared to control boys and girls, a finding similar to the main STRIP study, also supports the concordance between the substudy participants and the participants in the whole STRIP study (3). Thus, also the pubertal hormone data are likely to be generalisable. Secondly, the sample size in STRIP was powered to show differences in the serum cholesterol concentration between the study groups and not for showing differences in pubertal development in randomly selected subcohort.

CONCLUSION

Our findings support that dietary intervention with a low-saturated-fat and low-cholesterol diet during infancy and childhood is safe with respect to pubertal onset and maturation in both boys and girls as we found no evidence of altered function of the hypothalamic–pituitary–gonadal axis.

ACKNOWLEDGEMENTS

We thank Jorma Viikari, MD, PhD, Tapani Rönnemaa, MD, PhD, and Niels E. Skakkebaek, MD, PhD for providing insight and expertise that greatly assisted the research and for their comments that greatly improved the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

FINANCE

This work was supported by the Academy of Finland (grants no 251360, 276861, 253341, 258497, 308065, 307996), Sigrid Juselius Foundation, Turku University Hospital Special Governmental Grant, Foundation for Pediatric Research, Novo Nordisk Foundation (NNF16OC0021302).

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Anthropometric parameters, total cholesterol and saturated fat intake in the boy cohort.
Figure S2 Anthropometric parameters, total cholesterol and saturated fat intake in the girl cohort.
Table S1 Hormonal and anthropometric characteristics of the male participants: mean (SD).
Table S2 Hormonal and anthropometric characteristics of the premenarcheal female participants: mean (SD).
Table S3 Mean age of Tanner stages (G) among male participants.
Table S4 Mean age of Tanner stages (P) among male participants.
Table S5 Mean age of Tanner stages (B) among female participants.
Table S6 Mean age of Tanner stages (P) among female participants.
Data S1 List of abbreviations for supplemental tables.